

Remarks:

After entry of the amendment, claims 1-33, 35-48, 50-59, 61-70, 72-82, 84-87, 89-92 are pending.

The related applications section has been updated.

Claims 93-108 have been cancelled as they are directed to a non-elected invention. Applicants reserve the right to file divisional applications directed to the non-elected subject matter.

Claims 1 and 2 have been editorially amended and are supported by the specification at, for example, page 2, lines 29-33.

Claims 3, 4, and 74 have been amended to comply with the restriction requirement.

In claims 6, 7, 24, 25, 39, 40, 50, 51, 61, and 62, the term “characterized by” has been changed to “due to”.

Claim 6, 24, 39, 50 and 61 have been editorially amended to delete the term “preventing.”

Claims 33 and 91 have been amended and are supported by original claim 34. In view thereof, claim 34 has been cancelled and the dependency of claims 35 and 36 have been changed.

Claim 48 has been amended and is supported by original claim 49. In view thereof, claim 49 has been cancelled.

Claims 59 and 91 have been amended and are supported by original claim 60. In view thereof, claim 60 has been cancelled.

Claim 70 has been amended and is supported by original claim 71. In view thereof, claim 71 has been cancelled.

Claim 80 has been amended and is supported by original claim 83. In view thereof, claim 83 has been cancelled.

Claim 84 has been editorially amended to replace the term “preventing” with the term “treating.”

Claim 87 has been amended and is supported by original claim 88. In view thereof, claim 88 has been cancelled.

No issues of new matter should arise and entry of the amendment is respectfully requested.

A. Rejection under 35 U.S.C. §112, First Paragraph

Claims 6-73 and 76-92 are rejected under 35 USC § 112, first paragraph, as lacking enablement.

Applicants respectfully traverse the rejection and respectfully submit that the PTO has not established a *prima facie* case of lack of enablement to support a rejection under § 112, first paragraph.

MPEP 2164.01(b) states:

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U. S. C §112 is satisfied. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

MPEP 2164.02 states:

Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be “working” or “prophetic.” ... A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus **only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.**

MPEP 2164.02 states:

Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph does not turn on whether an example is disclosed.....An applicant need not actually reduce the invention to practice prior to filing.

MPEP 2164.04 states (emphasis added):

A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U. S.C. 112, first paragraph, **unless there is reason to doubt the objective truth** of the statements contained therein which must be relied on the enabling support.

[I] it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supportive disclosure and **to back up assertions of its own with acceptable evidence or reasoning** which is inconsistent with the contested statement.

The PTO asserts that there is no teaching in the prior art that nebivolol or nitric oxide have therapeutic utility in the treatment and/or prevention of vascular diseases. Applicants respectfully submit there are numerous publications that illustrate the role of nitric oxide in the treatment of numerous vascular diseases and disorders. In support thereof, Applicants refer to U.S. Patent 5,968,983 entitled “Methods and Formulations for Treating Vascular Disease”; U.S. Patent Nos. 6,165,975, 6,423,683 and 6,610,652 B2, all entitled “Microdose Therapy”; U.S. Patent Nos. 5,891,459, 6,337, 321 B1, 6,646,006 B2, all entitled “Enhancement of Vascular Function by Modulation of Endogenous Nitric Oxide Production or Activity”. At column 7, lines 20 to 35, U.S. Patent No. 6,646,006 states:

“vascular function is maintained or its deterioration inhibited or retarded by enhancing the level or activity of endogenous nitric oxide. By enhancing the level or activity of endogenous nitric oxide, common vascular degenerative diseases such as atherosclerosis, restenosis, hypertension, vasospasm, impotence, angina, and vascular thrombosis, can be treated prophylactically and/or therapeutically. The enhanced level or activity of nitric oxide (which is intended to include any precursor of nitric oxide which results in such enhanced level) can be achieved by modulating the activity, synthesis or concentration of any of the components associated with the formation of nitric oxide in the nitric oxide synthetic pathway, or inhibiting the rate of degradation of nitric oxide, its precursors, or the secondary messengers associated with the relaxation signal.”

In further support that nitric oxide is involved in the etiology of vascular disease, Applicants refer to U.S. Application No 2003/0212135 entitled “Pharmacotherapy for vascular dysfunction associated with deficient nitric oxide bioactivity.” U.S. Application No 2003/0212135 at paragraph [004], states (Emphasis added):

“It is known that **deficient nitric oxide bioactivity contributes to the pathogenesis of vascular dysfunctions**, including coronary artery disease, atherosclerosis, hypertension, diabetic vasculopathy and neurodegenerative

conditions stemming from ischemia and/or inflammation, and that such pathogenesis includes damaged endothelium, poor flow of oxygenated blood resulting in oxygen-deficient organs and tissues, elevated systemic vascular resistance (high blood pressure), vascular smooth muscle proliferation, progression of vascular stenosis and inflammation..”

Applicants respectfully submit that the PTO has not provided *any evidence or reason* to doubt the truth or accuracy of the statements in the application that the claimed nitric oxide enhanced nebivolol compounds are useful for treating or preventing vascular diseases. If the PTO maintains this rejection, Applicants respectfully request that the PTO *provide evidence in the form of scientific literature or publications* why one skilled in the art would doubt that the claimed compounds would be useful in the claimed methods.

In view of the above, Applicants respectfully submit that the claims satisfy the requirement under 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection under this provision be withdrawn.

B. Rejection under 37 C.F.R. §112, second paragraph

Claims 1, 2, 6, 7, 15, 19, 24, 25, 33, 34, 39, 40, 48, 50, 51, 59, 61, 62, 76, 78, 79, 80, 84, 87 and 90-92 are rejected under 37 C.F.R. §112, second paragraph, as being indefinite.

The rejections are addressed in the order in which they appear in the Office Action.

Claims 1 and 2 have been amended to clarify that the NO group, NO₂ group or the NO and NO₂ group is linked to the nebivolol and/or metabolite of nebivolol through an oxygen atom, a nitrogen atom or a sulfur atom.

In claims 6, 24, 39, 50, and 61, the term “preventing” has been deleted. Also, in these claims the term “characterized by” has been changed to “due to”.

In claims 7, 25, 40, 51, and 62, the term “characterized by” has been changed to “due to”.

In claims 15, 76, 90 and 92, Applicant respectfully submit that the PTO has already determined that the phrase “a compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase” satisfies the requirement under 35 USC §112, second paragraph. To this end, Applicants respectfully direct the Examiner’s attention to the claims (and supporting disclosure) in U.S. Patent Nos. 6,869,973 B2, 6,790,864 B2, 6,706,724 B2, 6,693,122 B2, 6,656,966 B2, 6,649,629 B2, 6,593,347 B2, 6,232,321, 6,221,881, 6,221,179,

6,197,782, 6,197,778, 6,177,428, 6,172,068, 6,172,060, 6,143,734, 6,133,272, 6,083,515, 6,057,347, 6,048,858, 6,043,233, 5,958,926, 5,703,073 and RE 37,234.

In claim 19, Applicants respectfully submit that the PTO has already determined that the specific compounds comprising at least one ON-O-, ON-N- or ON-C- group; or at least one O₂N-O-, O₂N-N-, O₂N-S- or -O₂N-C- group satisfies the requirement under 35 USC §112, second paragraph. To this end, Applicants respectfully direct the Examiner's attention to the claims (and supporting disclosure) in U.S. Patent Nos. 6,869,973 B2, 6,790,864 B2, 6,706,724 B2, 6,693,122 B2, 6,656,966 B2, 6,649,629 B2, 6,593,347 B2, 6,232,321, 6,221,881, 6,221,179, 6,197,782, 6,197,778, 6,177,428, 6,172,068, 6,172,060, 6,143,734, 6,133,272, 6,083,515, 6,057,347, 6,048,858, 6,043,233, 5,958,926, 5,703,073 and RE 37,234.

In claims 33 and 91, the antioxidant has been defined.

In claim 48, the specific nitrosated compounds have been defined.

In claims 59 and 91, the compounds used to treat cardiovascular diseases are specifically named.

In claim 70, the diuretic compounds have been defined.

Applicants respectfully submit that claims 78 and 79 satisfy the requirement under 35 U.S.C. §112, second paragraph. One skilled in the art would readily know which site to target based on the specific disease to be treated. The delivery of nitric oxide to the site can easily be assessed by any of the readily available analytical techniques used to monitor nitric oxide.

In claim 80, the medical device has been defined.

In claim 84, the term "preventing" has been deleted.

In claim 87, the specific injured tissue has been defined.

In view of the above, Applicants respectfully submit that the claims satisfy the requirement under 35 U. S. C. §112, second paragraph, and respectfully request that the rejections under this provision be withdrawn.

C. Rejection under 35 U.S.C. §103

Claims 1-92 are rejected under 35 U.S.C. § 103(a) as obvious over Van Lommen et al (U. S. Patent No. 4,654,362), in view of Loscalzo et al (U.S. Patent No. 6,635,273).

Applicants respectfully traverse the rejection and respectfully submit that the present claimed invention is unobvious over the cited references and there is no motivation to combine the cited references to arrive at the presently claimed invention. Applicants respectfully submit

that the cited references, individually or in combination, do not disclose or suggest, or provide motivation to arrive at the presently claimed invention.

As pointed out by the Examiner, Van Lommen does not disclose or suggest the presently claimed nebivolol compounds that comprise at least one NO and/or NO₂ group, and does not provide any motivation or incentive to add at least one NO and/or NO₂ group to nebivolol.

Loscalzo discloses a list of nitrosated compounds that could optionally be used in combination with an antioxidant and at least one of isosorbide mononitrate or isosorbide dinitrate to treat vascular diseases due to nitric oxide insufficiency. Loscalzo's list of nitrosated compounds includes angiotensin-converting enzyme inhibitors, beta-adrenergic blockers, calcium channel blockers, endothelin antagonists, angiotensin II receptor antagonists and renin inhibitors. Loscalzo does not provide any motivation or suggestion to select a β -adrenergic blocker as the particular nitrosated compound. Furthermore, there is no motivation or suggest in Loscalzo to select nebivolol as the specific beta-adrenergic blocker to treat vascular diseases due to nitric oxide insufficiency.

Von Lommen does not provide any motivation for one to treat or prevent a vascular disease due to nitric oxide insufficiencies by the administration of a nitrosated and/or nitrosylated nebivolol in combination with an antioxidant and isosorbide dinitrate and/or isosorbide mononitrate. Von Lommen does not even disclose antioxidants, isosorbide dinitrate and isosorbide mononitrate.

As the Federal Circuit stated in *Velandier v. Garner*, 68 USPQ2d 1769, 1772 (November 2003):

a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

The Patent Office has not established either factor as required by the Federal Circuit. The record is devoid of any suggestion that one of ordinary skill in the art would should make the presently nitrosated and/or nitrosylated nebivolol compounds or carry out the claimed methods. The mere

fact that references can be combined or modified does not render the combination obvious unless the prior art also suggests the desirability of the combination and a reasonable expectation for success. *Velandar* at 1772; MPEP § 2143.01.

It is respectfully submitted that the Patent Office has selected isolated teachings in references and combined them to arrive at a hindsight conclusion of obviousness based on the information described in the Applicants' own specification and claims. The Patent Office has not conducted a proper obviousness analysis, and has not established a *prima facie* case of obviousness based on the cited references. MPEP § 2143.01.

As mentioned above, the combination of Von Lommen and Loscalzo does not disclose, suggest or provide motivation to make or use the presently claimed nitrosated and/or nitrosylated nebivolol compounds alone or in combination with an antioxidant and/or isosorbide mononitrate and isosorbide dinitrate.

In view thereof, Applicants respectfully submit that the presently claimed invention is unobvious over the combination of cited references, and respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

D. Conclusion

Applicants respectfully request reconsideration and allowance of claims 1-33, 35-48, 50-59, 61-70, 72-82, 84-87, 89-92. The examiner is encouraged to contact the undersigned concerning any questions about the present application.

Respectfully submitted,



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